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Original Contribution

A Pooled Analysis of Second Primary Pancreatic Cancer

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Studies of pancreatic cancer in the setting of second primary malignant neoplasms can provide etiologic clues. An international multicenter study was carried out using data from 13 cancer registries with a registration period up to year 2000. Cancer patients were followed up from the initial cancer diagnosis, and the occurrence of second primary malignant neoplasms was compared with expected values derived from local rates, adjusting for age, sex, and period of diagnosis. Results from individual registries were pooled by use of a fixed-effects model. People were at higher risk of developing pancreatic cancer within 10 years of a diagnosis of cancers of the pharynx, stomach, gallbladder, larynx, lung, cervix, corpus uteri, bladder, and eye and 10 years or later following a diagnosis of cancers of the stomach, colon, gallbladder, breast, cervix, placenta, corpus uteri, ovary, testis, bladder, kidney, and eye, as well as Hodgkin's and non-Hodgkin's lymphomas. Pancreatic cancer was connected with smoking-related cancers, confirming the etiologic role of tobacco. The associations with uterine and ovarian cancers suggest that reproductive factors might be implicated in pancreatic carcinogenesis. The elevated pancreatic cancer risk in young patients observed among several types of cancer implies a role of genetic factors. Radiotherapy is also suggested as a risk factor.

neoplasms, second primary; pancreatic neoplasms; risk factors

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

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Pancreatic cancer is the 10th most common cancer in men and the 11th most common cancer in women worldwide (1). The incidence is highest in US Blacks and in several central European countries, with estimated age-standardized incidence rates up to 10 per 100,000 in men and 8 per 100,000 in women (2). In industrialized countries, the incidence rates are in the order of 8 and 5 per 100,000 in men and women, respectively, with little geographic variation (1). Pancreatic cancer is a rapidly fatal neoplasm: The median survival is 3–4 months, and there has been little improvement in recent decades (3).

Relatively little is known about the causes of pancreatic cancer. Increasing age, male sex, and familial history of pancreatic cancer are nonmodifiable established risk factors. Tobacco smoking is the only established modifiable risk factor with relative risks in the order of 2–3 (3). It was estimated that the proportions of population attributable risk were 27 percent for men and 11 percent for women in the world (4). Several nutritional factors are thought of as risk factors, including high intake of animal fat and total energy, low intake of fibers and vegetables, and heavy consumption of alcohol (3). A number of occupational exposures were also suspected as possible risk factors (5). In addition to chronic pancreatitis, other medical conditions such as diabetes, gallstones, and cholecystitis may also increase the risk of pancreatic cancer (3).

A second primary malignant neoplasm is a new neoplasm that is biologically independent of a preceding neoplasm. An excess of a second primary malignant neoplasm compared with an expected occurrence may arise from shared environmental or hereditary factors with the first neoplasm, from therapy-related exposure to chemical or physical carcinogens, or from intensive medical surveillance after the first cancer diagnosis (6). The study of second primary malignant neoplasms can, therefore, provide clues regarding etiologic factors of the second and the first neoplasms, particularly for neoplasms with limited etiologic information, such as pancreatic cancer. It can also contribute to identifying groups of patients who would require enhanced medical surveillance.

Studies of second primary malignant neoplasms based on individual cancer registries usually accumulated fewer second cancer cases, especially for infrequent neoplasms, and have less power to obtain reliable and robust results. We therefore organized an international multicenter study of second primary malignant neoplasms from high-quality cancer registries and used this large combined database to investigate which cancers are associated with pancreatic cancer. We hypothesized that this study would offer valuable clues and shed light on potential risk factors for pancreatic cancer. Because of the high fatality rate of the disease, we did not consider the occurrence of a second primary malignant neoplasm after pancreatic cancer.

MATERIALS AND METHODS

An international multicenter study of second primary malignant neoplasms was organized by inviting cancer registries that have been in operation for at least 25 years and have consistently been included in all the latest five volumes of *Cancer Incidence in Five Continents* (2) as an indicator of high-quality registration, including a high proportion of morphologic verification and a low proportion of cancers identified through death certificates only. Of an initial group of 19 contacted, 15 registries confirmed that the project was feasible and provided all necessary data. Two registries were subsequently excluded, because of discrepancies in the observed rates of second primary malignant neoplasms. The remaining 13 cancer registries include those from British Columbia, Manitoba, and Saskatchewan in Canada; Singapore; Slovenia; Norway; Denmark; Scotland in the United Kingdom; New South Wales in Australia; Sweden; Finland; Iceland; and Zaragoza in Spain. Registries from the United States were not included, because of the existence of a similar pooling project among the Surveillance, Epidemiology, and End Results (SEER) Program registries. The population covered by the registries at the end of the follow-up was approximately 46.9 million, with the smallest catchment population in Iceland (0.3 million) and the largest in Sweden (7.9 million).

Data for primary neoplasms occurring up to year 2000 were obtained, including identification number, month and year of birth, sex, date of diagnosis, topographic and morphologic codes of first primary malignant neoplasm, date of exit from the cohort (i.e., occurrence of a second primary malignant neoplasm, death, end of follow-up, or loss to follow-up), and status at exit from the cohort. Topographic and morphologic codes of subsequent primary malignant neoplasms were obtained. Systematic recoding of topography was conducted using the *International Classification of Diseases*, Ninth Revision (7). Third and subsequent primary neoplasms were not included in the present analysis. Person-years at risk were accumulated for each individual beginning at the time of diagnosis of the first malignant neoplasm and ending at exit, as defined above. Cancer registries may have different rules for defining when a tumor is an independent second primary malignant neoplasm, and these may have changed over time. The current analysis was based on the rules proposed by the International Association of Cancer Registries and the International Agency for Research on Cancer (8), which were applied to data from each cancer registry. In brief, a secondary primary cancer is an occurrence in one individual of a new malignant neoplasm that is biologically independent of the original primary cancer; that is, it is neither an extension nor a recurrence or a metastasis. Only one tumor shall be recognized in an organ or pair of organs or tissue.

Overall, the analysis included 7,060 patients who had been diagnosed with a second primary pancreatic cancer based on an observation of 18,102,415 person-years contributed by patients with all types of cancer except pancreatic cancer and nonmelanoma skin cancer (*International Classification of Diseases*, Ninth Revision, code 173). Denmark, Sweden, Norway, and Finland contributed 14–21 percent of first or second pancreatic cancer cases each, while Singapore, Zaragoza, and Iceland contributed altogether less than 3 percent of first or second pancreatic cancer patients. The distribution of first and second primary pancreatic cancer cases by sex, age, calendar period of cancer diagnosis, follow-up period since diagnosis of first cancer, and registry is displayed in table 1. The number of first primary malignant neoplasms ranged from 753 (placenta cancer) to 525,527 (female breast cancer) in the combined database.

The risk of developing a second primary pancreatic cancer was estimated separately for each cancer registry by calculating standardized incidence ratios following each other primary malignant neoplasm except for nonmelanoma skin cancer. It involved comparing the observed number of second primary pancreatic cancers with the expected number derived from 5-year age-, sex-, and calendar period-specific cancer incidence rates in the corresponding population. The test of significance and 95 percent confidence interval were calculated using an accurate asymptotic approximation to the Poisson distribution (9). The follow-up period was stratified into less than 1 year, 1–9 years, and 10 or more years since the first cancer diagnosis. Results from individual registries were pooled using the Mantel-Haenszel method to generate summary standardized incidence ratios in which the weights were proportional to the inverse of the variance of the standardized incidence ratio based on individual registries. This approach is based on a fixed-effects model (10). Sensitivity analysis was conducted by recalculation of summary standardized incidence ratios excluding particular individual registries.

RESULTS

The age-standardized incidence of pancreatic cancer as a first or a second cancer was higher in men than in women in all these registries. However, there were comparable numbers of female and male pancreatic cancer patients (table 1), because women contributed a higher number of person-years than did men.

Table 2 shows the standardized incidence ratios of pancreatic cancer following other primary malignant neoplasms overall and by follow-up period. Overall, the standardized incidence ratio of pancreatic cancer was increased significantly after cancers of the mouth, pharynx, stomach, gallbladder, larynx, lung, breast (both male and female), cervix uteri, placenta, corpus uteri, ovary, testis, bladder, kidney, and eye, as well as Hodgkin's disease and lymphoid leukemia. The risk of pancreatic cancer was decreased significantly after rectal and prostate cancers. However, after exclusion of the first year's follow-up, the change of standardized incidence ratio of pancreatic cancer following lung cancer, male breast cancer, prostate cancer, and lymphoid leukemia was not statistically significant.

The excess of pancreatic cancer was present within the first 12 months following cancers of the gallbladder, lung, ovary, and bladder but decreased significantly following cancers of the stomach, colon, rectum, and female breast. In the follow-up period 1–9 years after diagnosis of first primary malignant neoplasms, the occurrence of pancreatic cancer rose significantly following cancers of the pharynx, stomach, gallbladder, larynx, lung, cervix uteri, corpus uteri, bladder, and eye but fell significantly following rectal cancer. The risk was as high as 3.5-fold (standardized incidence

TABLE 1. Distribution of pancreatic cancer patients with a first or a second primary cancer by sex, age, follow-up since diagnosis of first cancer, calendar period at diagnosis, and registry, using data from 13 cancer registries with registration up to year 2000 in an international multicenter study

	Pancreatic cancer as a first cancer		Pancreatic cancer as a second cancer*	
	No.	%	No.	%
Sex				
Women	50,591	48	3,659	52
Men	55,180	52	3,401	48
Age (years) at cancer diagnosis				
<56	14,087	13	373	5
56–65	25,127	24	1,210	17
66–74	32,987	31	2,202	31
≥75	33,570	32	3,275	46
Follow-up period (years) since diagnosis of first cancer				
<1	91,924	87	983	14
1–4	11,739	11	2,239	32
5–9	1,056	1	1,646	23
≥10	1,052	1	2,192	31
Calendar period at cancer diagnosis				
Before 1975	26,656	25	755	11
1975–1983	27,818	26	1,515	21
1984–1990	25,088	24	2,002	28
1991 and later	26,209	25	2,788	39
Registry (registration period)				
Australia, New South Wales (1972–1997)	9,726	9	540	8
Canada, British Columbia (1970–1998)	4,980	5	562	8
Canada, Manitoba (1970–1998)	2,357	2	180	3
Canada, Saskatchewan (1967–1998)	1,654	2	201	3
Denmark (1943–1997)	19,316	18	1,470	21
Finland (1953–1998)	17,025	16	974	14
Iceland (1955–2000)	643	1	56	1
Norway (1953–1999)	18,413	17	1,054	15
Singapore (1968–1992)	1,108	1	5	0.1
Slovenia (1961–1998)	2,925	3	146	2
Spain, Zaragoza (1978–1998)	866	1	13	0.2
Sweden (1961–1998)	17,963	17	1,449	21
United Kingdom, Scotland (1975–1996)	8,795	8	410	6
Total	105,771	100	7,060	100

* Excluding those following nonmelanoma skin cancer (*International Classification of Diseases*, Ninth Revision, code 173).

TABLE 2. Observed number and standardized incidence ratio* of pancreatic cancer as a second primary cancer following other cancer types by follow-up period, using data from 13 cancer registries with registration up to year 2000 in an international multicenter study

First primary cancer sites (no. of first cancers)	Overall			<12 months			1–9 years			≥10 years			>1 year†		
	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval
Oral cavity, pharynx (ICD-9‡ codes 140–149) (n = 116,820)	346*	1.22*	1.09, 1.35*	41	1.23	0.88, 1.66	194*	1.25*	1.08, 1.44*	111	1.17	0.96, 1.41	305*	1.22*	1.08, 1.36*
Lip (ICD-9 code 140) (n = 35,351)	186	1.14	0.99, 1.32	14	1.02	0.56, 1.72	98	1.12	0.91, 1.36	74	1.21	0.95, 1.52	172	1.16	0.99, 1.34
Tongue (ICD-9 code 141) (n = 15,985)	27	1.12	0.74, 1.63	4	0.97	0.26, 2.48	18	1.29	0.76, 2.04	5	0.83	0.27, 1.94	23	1.15	0.73, 1.73
Salivary gland (ICD-9 code 142) (n = 11,108)	34	1.19	0.83, 1.67	5	1.79	0.58, 4.19	17	1.25	0.73, 2.01	12	0.99	0.51, 1.73	29	1.13	0.76, 1.62
Mouth (ICD-9 codes 143–145) (n = 22,378)	52*	1.34*	1.00, 1.76*	7	1.09	0.44, 2.24	32	1.39	0.95, 1.96	13	1.40	0.74, 2.39	45*	1.39*	1.01, 1.86*
Pharynx (ICD-9 codes 146–149) (n = 31,998)	47*	1.57*	1.15, 2.09*	11	1.72	0.86, 3.08	29*	1.70*	1.14, 2.44*	7	1.08	0.43, 2.23	36*	1.53*	1.07, 2.12*
Esophagus (ICD-9 code 150) (n = 52,589)	31	1.17	0.79, 1.66	16	1.38	0.79, 2.25	11	0.95	0.48, 1.70	4	1.17	0.32, 3.00	15	1.00	0.56, 1.65
Stomach (ICD-9 code 151) (n = 245,625)	283*	1.32*	1.17, 1.49*	37*	0.68*	0.48, 0.94*	171*	1.57*	1.35, 1.83*	75*	1.46*	1.15, 1.83*	246*	1.54*	1.35, 1.74*
Small intestine (ICD-9 code 152) (n = 10,946)	23	1.42	0.90, 2.13	6	2.30	0.84, 5.01	11	1.17	0.58, 2.09	6	1.44	0.53, 3.13	17	1.25	0.73, 2.00
Colorectal (ICD-9 codes 153 and 154) (n = 494,966)	850*	0.88*	0.82, 0.94*	117*	0.74*	0.61, 0.88*	469*	0.81*	0.74, 0.89*	264*	1.16*	1.02, 1.31*	733*	0.91*	0.85, 0.98*
Colon (ICD-9 code 153) (n = 298,766)	575	0.99	0.91, 1.08	76*	0.80*	0.63, 1.00*	336	0.96	0.86, 1.07	163*	1.21*	1.03, 1.41*	499	1.03	0.94, 1.13
Rectum (ICD-9 code 154) (n = 196,200)	275*	0.72*	0.63, 0.81*	41*	0.64*	0.46, 0.87*	133*	0.59*	0.49, 0.70*	101	1.08	0.88, 1.32	234*	0.73*	0.64, 0.83*
Liver, gallbladder, bile ducts (ICD-9 codes 155–156, except code 155.2) (n = 68,802)	65*	2.47*	1.91, 3.15*	24*	2.32*	1.48, 3.45*	33*	2.74*	1.88, 3.84*	8	2.07	0.89, 4.07	41*	2.57*	1.85, 3.49*
Liver (ICD-9 code 155, except code 155.2) (n = 29,811)	8	1.10	0.47, 2.16	7	1.96	0.79, 4.04	1	0.35	0.01, 1.95	0			1	0.27	0.01, 1.49
Gallbladder, bile ducts (ICD-9 code 156) (n = 38,991)	57*	3.00*	2.27, 3.89*	17*	2.50*	1.46, 4.01*	32*	3.48*	2.38, 4.91*	8*	2.67*	1.15, 5.26*	40*	3.28*	2.34, 4.47*

Table continues

TABLE 2. Continued

First primary cancer sites (no. of first cancers)	Overall			<12 months			1–9 years			≥10 years			>1 year†		
	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval
Peritoneum (ICD-9 code 158) (n = 5,423)	0			0			0			0			0		
Nose and nasal cavity (ICD-9 code 160) (n = 9,450)	23	1.30	0.82, 1.95	4	1.48	0.40, 3.79	16	1.64	0.94, 2.67	3	0.57	0.12, 1.66	19	1.26	0.76, 1.97
Larynx (ICD-9 code 161) (n = 40,190)	136*	1.29*	1.08, 1.52*	10	0.79	0.38, 1.45	88*	1.41*	1.13, 1.74*	38	1.23	0.87, 1.69	126*	1.35*	1.13, 1.61*
Lung (ICD-9 code 162) (n = 450,602)	311*	1.19*	1.06, 1.33*	127*	1.30*	1.08, 1.55*	151*	1.19*	1.01, 1.40*	33	0.89	0.61, 1.24	184	1.12	0.97, 1.30
Bone (ICD-9 code 170) (n = 12,328)	11	0.94	0.47, 1.69	1	0.74	0.02, 4.14	7	1.32	0.53, 2.72	3	0.60	0.12, 1.75	10	0.97	0.46, 1.78
Soft tissue sarcoma (ICD-9 code 171) (n = 26,285)	45	1.01	0.74, 1.35	5	0.97	0.31, 2.26	18	0.82	0.49, 1.30	22	1.25	0.79, 1.90	40	1.01	0.72, 1.38
Melanoma of skin (ICD-9 code 172) (n = 140,100)	262	1.00	0.88, 1.13	23	0.81	0.51, 1.22	141	0.96	0.81, 1.13	98	1.14	0.92, 1.39	239	1.02	0.90, 1.16
Female breast (ICD-9 code 174) (n = 525,527)	1,215*	1.10*	1.04, 1.17*	81*	0.69*	0.55, 0.86*	659	1.06	0.98, 1.14	475*	1.32*	1.20, 1.44*	1,134*	1.15*	1.09, 1.22*
Male breast (ICD-9 code 175) (n = 3,409)	18*	1.93*	1.14, 3.05*	4	2.97	0.81, 7.59	8	1.35	0.58, 2.65	6*	2.95*	1.08, 6.43*	14	1.76	0.96, 2.95
Cervix uteri (ICD-9 code 180) (n = 115,455)	369*	1.46*	1.32, 1.62*	18	1.33	0.79, 2.10	135*	1.69*	1.42, 2.00*	216*	1.36*	1.18, 1.55*	351*	1.47*	1.32, 1.63*
Placenta (ICD-9 code 181) (n = 753)	4*	5.77*	1.57, 14.8*	0			0			4*	6.60*	1.80, 16.9*	4*	5.82*	1.59, 14.9*
Corpus uteri (ICD-9 code 182) (n = 108,558)	408*	1.19*	1.07, 1.31*	20	0.77	0.47, 1.19	187*	1.16*	1.00, 1.34*	201*	1.28*	1.11, 1.47*	388*	1.22*	1.10, 1.35*
Ovary (ICD-9 code 183) (n = 107,038)	181*	1.40*	1.21, 1.62*	31*	1.78*	1.21, 2.52*	74	1.24	0.98, 1.56	76*	1.46*	1.15, 1.82*	150*	1.34*	1.14, 1.58*
Other female genital (ICD-9 codes 179 and 184) (n = 25,818)	55	1.05	0.79, 1.37	3	0.45	0.09, 1.31	32	1.17	0.80, 1.66	20	1.09	0.67, 1.68	52	1.14	0.85, 1.49
Prostate (ICD-9 code 185) (n = 357,253)	860*	0.94*	0.88, 1.00*	173	0.93	0.80, 1.08	615	0.96	0.88, 1.04	72	0.82	0.64, 1.03	687	0.94	0.87, 1.01
Testis (ICD-9 code 186) (n = 31,257)	83*	2.54*	2.02, 3.15*	1	0.74	0.02, 4.14	15	1.45	0.81, 2.40	67*	3.19*	2.47, 4.05*	82*	2.62*	2.08, 3.25*
Other male genital (ICD-9 code 187) (n = 7,297)	26	1.15	0.75, 1.68	2	0.75	0.09, 2.71	16	1.25	0.72, 2.04	8	1.11	0.48, 2.18	24	1.20	0.77, 1.79

Bladder (ICD-9 codes 188, 189.3, and 189.4) (*n* = 179,238)	638*	1.35*	1.25, 1.46*	102*	1.47*	1.20, 1.78*	402*	1.36*	1.23, 1.50*	134*	1.25*	1.04, 1.47*	536*	1.33*	1.22, 1.45*
Kidney (ICD-9 code 189, except codes 189.3 and 189.4) (*n* = 102,868)	212*	1.31*	1.14, 1.49*	30	1.16	0.78, 1.65	104	1.08	0.88, 1.31	78*	1.94*	1.54, 2.43*	182*	1.33*	1.15, 1.54*
Eye (ICD-9 code 190) (*n* = 13,606)	54*	1.64*	1.23, 2.14*	1	0.30	0.01, 1.66	30*	1.70*	1.15, 2.43*	23*	1.92*	1.22, 2.88*	53*	1.79*	1.34, 2.34*
Brain, nervous system (ICD-9 codes 191 and 192) (*n* = 72,516)	30	0.89	0.60, 1.26	5	0.76	0.25, 1.78	10	0.76	0.36, 1.39	15	1.06	0.59, 1.75	25	0.91	0.59, 1.35
Thyroid gland (ICD-9 code 193) (*n* = 39,002)	70	1.07	0.83, 1.35	6	1.10	0.41, 2.40	35	1.12	0.78, 1.56	29	1.00	0.67, 1.43	64	1.06	0.82, 1.36
Other endocrine gland (ICD-9 codes 164.0 and 194) (*n* = 5,303)	1	0.22	0.01, 1.21	0			0			1	0.64	0.02, 3.59	1	0.25	0.01, 1.38
Lymphohematopoietic (ICD-9 codes 200–208) (*n* = 298,928)	386*	1.16*	1.05, 1.28*	71	1.04	0.81, 1.31	223	1.07	0.93, 1.22	92*	1.67*	1.34, 2.04*	315*	1.19*	1.07, 1.33*
Lymphomas (ICD-9 codes 200–202) (*n* = 140,605)	195*	1.18*	1.02, 1.36*	25	0.86	0.56, 1.27	105	1.05	0.86, 1.28	65*	1.78*	1.37, 2.27*	170*	1.25*	1.07, 1.45*
Hodgkin's disease (ICD-9 code 201) (*n* = 31,154)	45*	1.80*	1.31, 2.41*	2	0.64	0.08, 2.31	18	1.44	0.85, 2.27	25*	2.67*	1.72, 3.93*	43*	1.96*	1.42, 2.65*
Non-Hodgkin's lymphoma (ICD-9 codes 200 and 202) (*n* = 109,451)	150	1.07	0.91, 1.25	23	0.89	0.56, 1.33	87	1.00	0.80, 1.23	40*	1.47*	1.05, 2.00*	127	1.11	0.93, 1.32
Multiple myeloma (ICD-9 code 203) (*n* = 50,051)	66	1.12	0.86, 1.42	17	1.08	0.63, 1.73	42	1.09	0.79, 1.48	7	1.44	0.58, 2.96	49	1.13	0.84, 1.50
Leukemias (ICD-9 codes 204–208) (*n* = 108,272)	125	1.16	0.97, 1.38	29	1.24	0.83, 1.78	76	1.08	0.85, 1.35	20	1.46	0.89, 2.25	96	1.14	0.92, 1.39
Lymphoid leukemia (ICD-9 code 204) (*n* = 47,651)	94*	1.24*	1.00, 1.51*	22	1.55	0.97, 2.35	58	1.11	0.84, 1.43	14	1.46	0.80, 2.46	72	1.16	0.91, 1.46
Myeloid leukemia (ICD-9 code 205) (*n* = 33,892)	10	0.62	0.30, 1.13	4	0.71	0.19, 1.82	6	0.64	0.24, 1.40	0			6	0.57	0.21, 1.23
Other leukemia (ICD-9 codes 206–208) (*n* = 26,729)	21	1.37	0.85, 2.09	3	0.83	0.17, 2.43	12	1.37	0.71, 2.39	6	2.03	0.75, 4.43	18	1.53	0.91, 2.42

* Those whose 95% confidence interval does not include one.
† Excluding second pancreatic cancer observed within the first 12 months.
‡ ICD-9, *International Classification of Diseases*, Ninth Revision.

ratio (SIR) = 3.48, 95 percent confidence interval (CI): 2.38, 4.91) following gallbladder cancer and less than twofold following other cancers. After 10 or more years of follow-up, the standardized incidence ratio of pancreatic cancer was elevated significantly after cancers of the stomach, colon, gallbladder, female and male breast, cervix uteri, placenta, corpus uteri, ovary, testis, bladder, kidney, and eye, as well as Hodgkin's and non-Hodgkin's lymphomas. In this period, the risk of pancreatic cancer increased approximately twofold after kidney and eye cancers; threefold after cancers of the gallbladder, male breast and testis, and Hodgkin's disease; and sevenfold after cancer of the placenta. The risk of pancreatic cancer was no longer reduced after 10 or more years of a diagnosis of rectal cancer.

To explore the etiologic clues in more detail, we performed an additional analysis stratifying by sex, follow-up by sex, age, and calendar period at first cancer diagnosis. The standardized incidence ratios of pancreatic cancer were comparable between women and men after all these cancers except lung cancer (for women: SIR = 1.49, 95 percent CI: 1.18, 1.87; for men: SIR = 1.11, 95 percent CI: 0.89, 1.27) and eye cancer (for women: SIR = 1.52, 95 percent CI: 0.96, 2.31; for men: SIR = 1.73, 95 percent CI: 1.18, 2.44), after which the risk of pancreatic cancer increased significantly only among women and men, respectively. The elevated risk of pancreatic cancer after stomach, gallbladder, lung, female and male breast, cervical, ovarian, kidney, and eye cancers, as well as Hodgkin's disease, was more evident in young patients, and the reduced pancreatic cancer risk was restricted to older rectal cancer patients (table 3). The standardized incidence ratios of pancreatic cancer after cervical cancer tended to increase linearly toward more recent calendar periods from 1.36 (95 percent CI: 1.19, 1.54) before 1975 to 2.50 (95 percent CI: 1.51, 3.91) after 1991 with a significant trend ($p = 0.002$). Stratified analysis of other first neoplasms did not reveal any noticeable pattern. Sensitivity analysis indicates that withdrawal of data from any particular registry had little impact on either the significance tests or the summary standardized incidence ratios (results not shown).

DISCUSSION

We have conducted the largest analysis of pancreatic cancer as a second primary neoplasm. Previous studies of pancreatic cancer in the setting of second cancer (11–14), however, were hampered by small numbers of first cancers, thus reducing the capacity of comparing the pattern of associations with neoplasms occurring before pancreatic cancer. Generally, cancer with high incidence and long survival has more person-years to provide higher power in our study. Most significant findings in the study have satisfactory power (>80 percent) based on the observed and expected occurrences apart from mouth cancer, cancer of the placenta, prostate cancer, lymphomas, and lymphoid leukemia as a result of low incidence (placenta) or small standardized incidence ratios (mouth, prostate, lymphomas, and lymphoid leukemia). Our study, with its large power, put forward some important risk factors for pancreatic cancer.

TABLE 3. Observed number and standardized incidence ratio* of pancreatic cancer following selected cancer types, by age at first cancer diagnosis, using data from 13 cancer registries with registration up to year 2000 in an international multicenter study

	<56 years			56–65 years			66–74 years			≥75 years			
	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	Observed no.	Standardized incidence ratio	95% confidence interval	p_{trend}
Stomach (ICD-9† code 151)	62*	2.71*	2.08, 3.47*	90*	1.67*	1.34, 2.05*	73	0.96	0.75, 1.20	58	0.96	0.73, 1.24	<0.001
Rectum (ICD-9 code 154)	36	0.96	0.67, 1.33	82	0.81	0.65, 1.01	93*	0.65*	0.52, 0.80*	64*	0.63*	0.48, 0.80*	0.02*
Gallbladder, bile ducts (ICD-9 code 156)	10*	8.00*	3.83, 14.7*	16*	3.78*	2.16, 6.13*	17*	2.42*	1.41, 3.88*	14*	2.16*	1.18, 3.63*	0.002
Lung (ICD-9 code 162)	38*	1.52*	1.07, 2.08*	137*	1.68*	1.41, 1.98*	82	0.81	0.65, 1.01	54	1.00	0.75, 1.30	<0.001
Female breast (ICD-9 code 174)	362*	1.48*	1.33, 1.64*	319	1.08	0.97, 1.21	320	0.98	0.88, 1.09	214	0.92	0.80, 1.05	<0.001
Male breast (ICD-9 code 175)	5*	4.66*	1.51, 10.9*	6	2.42	0.89, 5.27	5	1.54	0.50, 3.59	2	0.79	0.10, 2.86	0.02
Cervix uteri (ICD-9 code 180)	205*	1.54*	1.34, 1.76*	94*	1.43*	1.15, 1.75*	54*	1.39*	1.05, 1.82*	16	1.10	0.63, 1.79	0.19
Ovary (ICD-9 code 183)	64*	1.73*	1.33, 2.21*	56*	1.40*	1.06, 1.82*	47*	1.38*	1.01, 1.83*	14	0.78	0.43, 1.31	0.01
Kidney (ICD-9 code 189)	46*	1.89*	1.39, 2.53*	65*	1.32*	1.02, 1.68*	67	1.18	0.92, 1.50	34	1.05	0.73, 1.47	0.01
Eye (ICD-9 code 190)	19*	2.49*	1.50, 3.90*	12	1.22	0.63, 2.13	14	1.38	0.75, 2.31	9	1.69	0.77, 3.20	0.25
Hodgkin's disease (ICD-9 code 201)	25*	2.53*	1.64, 3.74*	11	1.59	0.79, 2.84	5	0.92	0.30, 2.15	4	1.43	0.39, 3.65	0.04

* Those whose 95% confidence interval does not include one.

† ICD-9, *International Classification of Diseases*, Ninth Revision.

Tobacco smoking is an established risk factor for pancreatic cancer, which therefore was expected to be connected with tobacco-related cancers. The standardized incidence ratio of pancreatic cancer increased significantly among both women and men following cancers of the pharynx, larynx, stomach, and bladder, as well as cervical cancer. The standardized incidence ratio was more stable when several smoking-related cancers (cancers of the head and neck, lung, bladder, and kidney) were grouped (for women: SIR = 1.33, 95 percent CI: 1.20, 1.47; for men: SIR = 1.26, 95 percent CI: 1.19, 1.33). However, the standardized incidence ratio of pancreatic cancer following lung cancer was elevated significantly only among female patients, not male patients. That may be due to the low relative risk of smoking for pancreatic cancer or to a histologic shift for long-term survivors as a result of the high mortality of lung cancer. Such a gender difference has been found in another study (13). Nevertheless, tobacco smoking is not likely to entirely explain the clustering of pancreatic cancer with these smoking-related cancers, in consideration of two facts: 1) These standardized incidence ratios were not proportional to the well-known relative risks of smoking for these cancers, for example, high relative risks of smoking for lung cancer and low standardized incidence ratios of pancreatic cancer following lung cancer; 2) there was no association with other smoking-related cancers, for example, esophageal cancer.

The excesses of pancreatic cancer after uterine and ovarian cancers within 1–9 years suggest shared risk factors. A similar chronologic pattern of standardized incidence ratios of pancreatic cancer after ovarian cancer has been found in another study (15). The role of reproductive factors, especially nulliparity, as common denominators is indicated (16). Although research results are inconsistent (17–19), the role of reproductive factors in pancreatic cancer etiology has been suggested from the cumulated evidence, for example, high serum estrogen levels in pancreatic cancer patients (20), inverse association with the number of pregnancies (21, 22), the growth inhibition on the pancreas, and the therapeutic effects on pancreatic cancer of tamoxifen (23, 24). Additionally, the borderline reduction of pancreatic cancer following prostate cancer possibly points to androgens as a common cause (25). Because the complex pattern and relation between reproductive factors and hormones have not been well known, the mechanism and underlying hormonal factors for pancreatic cancer need to be clarified.

Familial pancreatic cancer susceptibility explains a fraction of the overall pancreatic cancer incidence (26). Pancreatic cancer is associated with familial clustering (14) and is a phenotype of several familial cancer syndromes, for example, hereditary breast/ovarian cancer (BRCA2), Peutz-Jeghers syndrome, Li-Fraumeni syndrome, p16-linked melanoma-pancreatic cancer, familial pancreatitis, and hereditary nonpolyposis colorectal cancer (HNPCC) (27). Sporadic genetic alterations also account for some of the pancreatic cancer cases (26). Associations between pancreatic cancer and particular cancers would be suggestive of a common genetic predisposition if they were more pronounced in young patients. The standardized incidence ratio of pancreatic cancer was particularly elevated among young patients with a cancer of the stomach, gallbladder, lung, female breast, male breast, eye, ovary, or testis. Investigating further these associations might provide important etiologic clues for pancreatic cancer. For example, the special clustering pattern between male breast cancer and pancreatic cancer points to a common genetic factor: *BRCA2* mutations (28).

The improved cancer therapies and the resulting improvement in survival enhance the risk of a therapy-induced second primary malignant neoplasm, for both local (e.g., in radiotherapy-irradiated fields) and systemic (e.g., after hormone or chemotherapy) treatments. In our study, the standardized incidence ratio of pancreatic cancer was raised significantly after 10 years of diagnosis of cancers of the stomach, colon, gallbladder, breast, cervix uteri, placenta, corpus uteri, ovary, testis, bladder, kidney, and eye, as well as Hodgkin's and non-Hodgkin's lymphomas. Similar associations have been observed by others for stomach (29), ovary (14, 30), breast and cervix (14, 31), kidney (14), and bladder and testicular cancers (14, 32, 33). Medical treatment may explain such associations, because they emerged only a long time after diagnosis of the first malignant neoplasm. A lengthy latent period is believed to be necessary for therapeutic factors to cause a new malignant neoplasm. Radiotherapy plays an important role in treating some of these malignant neoplasms and may be the principal factor for the clusterings, since pancreatic cancer risk has been found to be increased after radiation treatment for cervical (34) and testicular cancers (32) and after radiotherapy for nonneoplastic medical conditions (35, 36). On the other hand, chemotherapy may also increase the risk of pancreatic cancer (37), but its possible effects need to be investigated further.

The positive association between gallbladder cancer and pancreatic cancer may be partly due to misdiagnosis of pancreatic cancer, but the high standardized incidence ratio cannot be fully explained by it. Besides the common genetic traits with such an association, chemicals and occupational exposures, particularly medical conditions of the gallbladder including gallstones, cholecystectomy, and cholecystitis, may be the shared determinants (38–40). Pancreatic cancer clustered with some other cancers, but the reasons remain unclear. The deficit of pancreatic cancer after rectal cancer in both sexes is interesting and was also observed in Connecticut and Denmark (11, 12). It may imply common but counteractive determinants that raise the risk of one type of malignant neoplasm but reduce the risk of another one, although the determinants remain to be discovered. It also suggests etiologic heterogeneity between colon and rectal cancer (41). The risk of pancreatic cancer was high 1 year after the diagnosis of eye cancer. The majority of eye cancer is uveal melanoma, and little is known about its risk factors. Genetic factors and occupational exposures may lead to such a connection (14, 42). Dietary factors in combination are very important for most neoplasms including pancreatic cancer, and they may account in part for these observed associations. Due to the complex pattern of dietary factors and their uncertain and weak impact on pancreatic cancer, it is difficult to make any inferences for specific factors.

Biases may account for some of the associations observed in our study. An immediate excess of second primary malignant neoplasms is a common phenomenon due to enhanced medical surveillance for cancer patients. In fact, they are often synchronous neoplasms and are detected by enhanced physical examination and surveillance immediately after initial tumor diagnosis. Therefore, the first year of follow-up was analyzed and explained separately. The second pancreatic cancer may be a recurrence/extension or a metastasis of the first primary neoplasm, for example, gallbladder. It was found that 10 percent of patients diagnosed with pancreatic cancer actually had another disease that mimics it (43). Such misdiagnosis can cause false positive associations and has to be considered in explaining the results. Exclusion of the first 12-months' follow-up would lessen the impact of this bias. In addition, the quality of diagnosis may be different across age groups. It was found that accuracy of diagnosis of pancreatic cancer decreased with increasing age (44), which might attenuate the clustering of pancreatic cancer following particular cancers in older patients.

This analysis was based on the pooling of data from 13 registries, and some level of heterogeneity is inevitable, as a result of chance, varying incidence of neoplasms and important risk factors, different underlying treatment and exposure characteristics, and particular cancer registry characteristics. Such heterogeneity may lead to variable effect size estimates. Heterogeneity was identified in some of the pooled results and, to some extent, could explain the observed associations. However, the pooled standardized incidence ratios were quite robust on the basis of the sensitivity analysis. Heterogeneity in the incidences of neoplasms and their risk factors exists among registries but also within a registry. The expected number of cases was calculated by use of incidence data from respective cancer registries, which would lessen the heterogeneity of incidence of neoplasms across registries. Heterogeneity in cancer registry characteristics was minimized by ensuring that there was a common protocol among the registries for reporting second primary malignant neoplasms, undertaking detailed comparison of results for discrepancies, and dropping two registries because of apparent underreporting in one instance and overreporting in the other. Nordic countries, which have continuously collaborated over several decades, contribute many more pancreatic cancer cases (~70 percent) than any of the other registries. The results were driven by these large registries and would veil the data to some extent obtained from other registries. On the other hand, homogeneity across the four large registries made the pooled results stable and reliable.

Information on histologic type and therapy was not available in this study, which restricts our ability to investigate the associations between pancreatic and other cancers. The clustering between lung cancer and pancreatic cancer was confined to females. It may imply shared risk factors with lung adenocarcinoma only because the majority of pancreatic cancer is adenocarcinoma, and it is more common among female lung cancer patients. The trend of higher standardized incidence ratios of pancreatic cancer in more recent periods following cervical cancer is also suggestive of different risk factors for different histologic subsets, in that the adenocarcinoma of cervical cancer is becoming increasingly common (45). In addition, attributing elevated pancreatic cancer risk to radiotherapy 10 years after the diagnosis of other cancers is based on inference with uncertainty, because we did not collect therapy information.

To our knowledge, this study is the largest analysis of pancreatic cancer as a second primary malignant neoplasm. It revealed a complex pattern of associations between pancreatic cancer and other malignant neoplasms, including several rare cancers which cannot be adequately studied in smaller populations. Our study provides potentially important etiologic leads. Smoking is a risk factor for pancreatic cancer, as it clustered with smoking-related cancers including cancers of the pharynx, larynx, lung, stomach, and bladder. Reproductive factors might be implicated, in that pancreatic cancer was associated with uterine and ovarian cancers. The elevated pancreatic cancer risk in young patients with several types of cancer is suggestive of a role of genetic factors.

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